REMARKS

Upon entry of the amendments herein, claims 1-9 and 12-28 remain pending in the application. Claim 1 has been amended herein. No new matter has been introduced by the amendments.

The Examiner has objected to the pending claims as containing nonelected subject matter; the Examiner notes that Formula I encompasses compounds other than those wherein R_1 is a pyridyl moiety. Applicants acknowledge their election of restriction group II and that the Examiner may have had basis at the time for invoking nonconformity with PCT Rules 13.1 and 13.2 as justification for leveling a restriction requirement in the first place. However, the presence of prior art reading on the claims notwithstanding, the Examiner's division of the subject matter into nine restriction groups was arbitrary. It was Applicants' understanding that their election of a particular subgroup from the definition of substituent R_1 would serve as the basis for an initial search but that the possibility remained of expansion of the search once the patentability of the elected subgenus of compounds had been determined. Furthermore, Applicants wish to point out that, in light of the amendments herein to claim 1, the cited prior art no longer reads on any of the compounds encompassed by the instant base claim (see more

below), and all of the compounds encompassed by the amended claim must be said to be linked by a special technical feature. In other words, the Examiner's original reasons for leveling a restriction requirement are no longer applicable. Still further, Applicants have provided herein (again, see below) data showing the effectiveness of compounds of formula I wherein R_1 is pyridyl, as well as compounds wherein R_1 is other than pyridyl. For all the reasons set forth above, the Examiner's objection is premature at best. It is requested that this objection be withdrawn or at least held in abeyance until such time as the scope of allowable subject matter is more clearly determined.

The Examiner asserts that, in view of the restriction, the present title is no longer descriptive and requires amendment. Applicants disagree with the assessment. In the first place, as set forth above, it is believed that the limitation of the scope of the compounds to ones wherein R_1 is a pyridyl moiety is premature at best. Secondly, even if the scope of compounds presently mandated by the Examiner were maintained, the definition of substituent R_3 remains such that by no means can all compounds be categorized as carboxylic acid derivatives. At such time as the scope of allowable subject matter is finally decided, Applicants will consider amending the title.

The Examiner has deemed improper Applicants' incorporation by reference of two general articles providing details of assay conditions for the instantly claimed compounds; the Examiner requires that the specification be amended to include the "essential" material incorporated by reference. Applicants have complied with this requirement by amendment of the specification herein by addition of details of the assay procedures from the cited references. The undersigned agent for Applicants hereby states that the amendatory material is the same assay material referred to in the specification as originally filed and attributed to the two references cited therein on page 18, lines 21-24.

Claims 1-9, 2-17 and 19-28 have been rejected under 35 USC §112, second paragraph as being indefinite. The Examiner cites page 6, line 24 as defining heterocyclyl as substituted or unsubstituted but asks the question: "Substituted by what?" The answer to this question is clearly provided on page 8, lines 6-11 of the instant specification. It may be true that the claims measure the invention, but it is also true that the terms used in the claims are clearly defined in the specification. Accordingly, this rejection should be withdrawn.

Claim 18 has been rejected as indefinite for reciting a limitation for which there is no antecedent basis in the base

claim from which it depends. Claim 1 has been amended to recite that all of the nitrogen-containing aromatic heterocyclyl groups from which R_1 may be selected are substituted with one or more basic groups. Support for this amendment can be found in the disclosure of the specification running from page 6, line 24 to page 7, line 4 and on page 8, lines 6-11.

Claims 1-9 and 12-28 have also been rejected as indefinite for reciting the phrase "carboxylic acid isostere". Claim 1 has been amended to more particularly define what is meant by this phrase. Support for this amendment can be found on page 5, lines 29 and 30 of the instant specification.

Claims 12, 13, 16 and 17 have been rejected under 35 USC §112, first paragraph; the Examiner asserts that the specification does not provide sufficient enablement for treating "conditions associated with inhibition of carboxypeptidase U." The Examiner further asserts that no testing data are provided and that details of the assay itself have not been properly disclosed. The latter criticism has been addressed, as set forth above, by Applicants' amendment of the specification. Using the assay procedures now detailed in the specification, Applicants obtained data for most of the examples disclosed in the instant specification. These data are set forth in the table below:

Example	pIC_{50} CPU at pH 7.4 (*= pH 8)
Example 1	5.5*
Example 3	3.4*
Example 4	3.3*
Example 5	5.5*
Example 6	6.6
Example 7	6.2*
Example 8	3.6*
Example 9	5.8
Example 10	2.7*
Example 11	4.0*
Example 12	3.9*
Example 13	4.8*
Example 14	6
Example 15	5.1
Example 16	5.1
Example 17	5.9
Example 18	5.2
Example 20/A	4
Example 20/B	5.4
Example 20/C	6.4
Example 20/D	5

Example	pIC_{50} CPU at pH 7.4 (*= pH 8)
Example 21/A	5
Example 21/B	4
Example 21/C	6.3
Example 21/D	4.5
Example 22	5
Example 23	4.9
Example 24	5.8
Example 25	6
Example 26	5.4
Example 27/A	6.1
Example 27/B	4.9
Example 27/C	6.1
Example 27/D	5.7
Example 28	5.7
Example 29	5
Example 30	5.2
Example 31	6.1
Example 33	5.7
Example 34	5.9

From the data, it can be seen that the exemplified compounds of the instant invention uniformly have high PIC_{50} values, thus indicating that they are potent inhibitors of carboxypeptidase U. The large number of examples shown to be effective is more than adequate to enable the present scope of the claims. Furthermore, particularly in light of the data, one of skill in the art would find credible the assertion that the instant compounds would be effective in the treatment of any condition "associated with inhibition of carboxypeptidase U." The rejcction should be withdrawn.

A second rejection of claims 12, 13, 16 and 17 under 35 USC §112, first paragraph has been leveled. The Examiner asserts that these claims are not sufficiently enabled by the disclosure of the specification with regard to prevention of diseases. Applicants disagree with this assertion.

In the first place, the Examiner is again referred to the data set forth above showing the potency of a wide range of the instant compounds in inhibiting CPU. Just as one of skill in the art would find credible, based on these data, the assertion that the instant compounds can be effective in treating preexisting conditions, so too would the artisan find credible the assertion that such conditions could be prevented by administration of the instant compounds, which compounds inhibit

the activity of an enzyme which is known by said activity to be linked to the disease conditions disclosed.

The Examiner refers to the passage in the instant specification running from page 17, line 1 to page 18, line 5, wherein are disclosed the diseases to be treated. For one thing, the Examiner is referred to the paragraph on page 17, lines 26-29, wherein are disclosed some reasonable expectations of the utility of the instant compounds in prophylaxis. The compounds of the invention are further disclosed to be useful for conditions wherein there is an undesirable excess of proCPU/CPU.

The expectation of the onset of such phenomena as reocclusion, restenosis and rethrombosis after, for example, various surgical procedures is perfectly reasonable; one would not have to spend an inordinate amount of time searching for susceptible patients as the Examiner has suggested. Furthermore, it would be routine and well within the time available to a practitioner to measure excesses of proCPU/CPU as an indication of susceptibility to conditions associated with CPU. The Examiner asserts that it would be necessary to ascertain which individuals <u>will</u> develop the claimed diseases. However, it would only be necessary, at most, to identify those that <u>might</u> develop said diseases.

This would be similar to, for example, the monitoring of blood pressure as a means of anticipating the development of possible associated diseases in the future. One can monitor blood pressure and, noting that blood pressure is higher than desirable, can administer drugs to prevent conditions such as stroke which are known to arise from a condition of high blood pressure. The Examiner asserts that "the only established prophylactics are vaccines...." However, the administration of blood-pressure-lowering drugs, which are not vaccines, can be viewed as a method of prophylaxis of conditions brought about by high blood pressure.

Thus, similarly, and contrary to the Examiner's assertion, there are a number of conditions for which it might be easily be determined that inhibition of CPU activity in advance of an actual detectable condition would be beneficial. This rejection should be withdrawn.

The Examiner has leveled three anticipation rejections. In each case the Examiner asserts that the cited reference discloses a compound of the instant genus wherein R_1 is an unsubstituted pyridine moiety. As pointed out above, in Applicants' response to the indefiniteness rejection of claim 18, claim 1 has been amended to make clear that all of the nitrogen-containing aromatic heterocyclyl groups from which

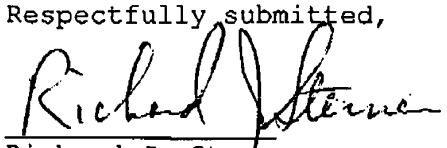
substituent R_1 may be selected are substituted by one or more basic groups. This amendment renders moot the three prior art rejections leveled by the Examiner. Again, support for this amendment to claim 1 can be found in the instant specification from page 6, line 24 to page 7, line 4 and on page 8, line 6-11.

The Examiner has indicated the claims 7-9, 14, 15 and 18-28 would be allowable if amended to address the rejections under 35 USC §112, second paragraph and to eliminate their dependence from rejected claims. Applicants maintain that, in light of the amendments and arguments herein, all pending claims are allowable. The only remaining issue would appear to be the ultimate scope of subject matter that will be passed to allowance. The Examiner is urged to contact the undersigned to discuss the final disposition of this application.

The Commissioner is hereby authorized to charge any fees which may be due in connection with this communication to Deposit Account No. 23-1703.

Dated: January 12, 2004

Respectfully submitted,



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